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Canine chronic renal disease: Prevalence and types of glomerulonephritis in the dog

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Canine chronic renal disease: prevalence and types of glomerulonephritis in the dog. In a prospective survey, one hundred and eleven dogs with canine chronic renal disease, presenting to 24 veterinary practices in East Anglia and the West Midlands (geographical area 8,600 square miles) were identified. More than 20 different breeds were represented. In 76 cases, clinical details, blood and urine biochemistry, serology and kidney tissue for light and electron microscopy, and immunohistochemistry were obtained. Forty (52%) had glomerular (GN) and 36 (48%) non-glomerular (NGN) disease. Types of GN identified were (W.H.O. classification, number of cases in brackets): focal glomerulonephritis (gn) (5), diffuse mesangial proliferative gn (8), diffuse endocapillary proliferative gn (2), mesangiocapillary gn type I (8), diffuse crescentic gn (1), diffuse sclerosing gn (7), amyloid (6), unclassifiable gn (3). Eight dogs with GN and 13 with NGN had extra-renal lesions. In only one GN case (bacterial endocarditis) was the etiology clear. Proteinuria, but not age, breed, sex, serum creatinine or hematuria, discriminated between GN and NGN groups. This prospective survey identifies GN, with morphological types as found in humans, as a common cause of canine chronic renal disease.

Until about 15 years ago chronic renal disease in the dog was attributed mainly to 'chronic interstitial nephritis' [1, 2]. Glomerulonephritis, although recognized [2–5], was considered relatively unimportant. More recently a number of case reports and series have emphasized the importance of canine glomerular pathology [6–11] and shown that glomerulonephritis (gn) is found in cases previously described as 'chronic interstitial nephritis' [12, 13]. Murray and Wright [8] have classified 42 cases of canine gn from postmortem material and others have studied dogs presented for euthanasia [9, 10] or kept for research [14]. However, the true incidence of gn as a cause of renal disease is not known, the unpublished data available from veterinary school referrals inevitably being biased towards particular research interests. The present study is a prospective survey designed to provide data on the prevalence, possible etiologies and pathology of canine chronic renal disease (CCRD), and in particular to classify spontaneously occurring canine gn. This paper reports the pathological findings and relevant clinical details in 76 dogs with significant renal pathology. Other findings from the survey are being published separately.

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Methods

Design of survey

Selection of practices. Twenty-four veterinary practices specializing in canine and feline medicine, and representing 20% of practices in East Anglia and approximately 30% of practices in the South East Midlands (a geographical area of approximately 8,600 square miles including urban and rural areas), agreed to collaborate in the survey. The main survey period was one year (from February 1980).

Selection of cases. Practices were asked to report suspected cases of CCRD on the basis of the following clinical criteria: polydipsia, polyuria, anorexia, vomiting, wt loss, halitosis and urine testing for protein. Cases of suppurative endometritis (pyometra) and diabetes mellitus were to be excluded as these are known to be associated with well recognized glomerulopathies [5].

Investigation of suspected cases. Blood, urine and Microstix III–Ames (for bacteriology) were sent to the Renal Unit at the Animal Health Trust, together with further clinical details. The following investigations were performed: plasma urea and creatinine and urinary protein, fibrin degradation products (FDPs) [15] and microscopy [18]. Aliquots of plasma were stored for leptospira and adenovirus serology, DNA binding and complement studies. Antibodies to leptospira were determined by a microtitre plate modification of the microscopic agglutination test (MAT) using live antigens [16]. Antibodies to adenovirus were measured semiquantitatively using an improved counter-electrophoresis method [17] with a bulked tissue culture derived antigen (Glaxo, U.K.).

Renal histology

Renal tissue from 76 dogs was examined by light microscopy. Tissues were fixed in buffered formalin, and paraffin embedded. 3 μ sections were stained with hematoxylin and eosin, periodic-acid–Schiff, and Martius Scarlet Blue trichrome stain. Where amyloid was suspected, a Congo Red stain was done on 8 μ sections.

Immunohistochemistry

Initial screening for IgG, C3 and fibrin related antigen (FRA) was carried out by direct immunofluorescence using commercial antisera [18] in five cases and by indirect immunoperoxidase on buffered formalin fixed tissue in 71 cases. Subse-

Table 1. Pathological and clinical findings in 76 dogs with CCRD.

	No. of cases	Sex M:F	Mean age at presentation *months* ± SEM	Mean duration of illness *weeks*[a] ± SEM	Mean proteinuria *g/liter*[b] ± SEM	Hematuria[c]	FDPs[c]	Mean serum creatinine *μmole/liter* ± SEM
Glomerular disease (40 cases)								
Focal gn	5	2:3	80 ± 21	58 ± 22	2.2 ± 0.7	2/5	2/5	366 ± 145
Diffuse mesangial proliferative gn	8	6:2	126 ± 21	6 ± 3	2.3 ± 0.4	4/7	4/7	425 ± 143
Diffuse endocapillary proliferative gn	2	2:0	114 ± 66	8 ± 5	1.1 ± 0.2	2/2	1/2	187 ± 39
MCGN Type I	8	3:5	107 ± 16	6 ± 2	4.0 ± 0.7	6/8	8/8	627 ± 178
Diffuse crescentic gn	1	0:1	7	3	*	*	*	231
Diffuse sclerosing gn	7	6:1	94 ± 23	4 ± 2	4.9 ± 1.3	2/6	5/6	504 ± 91
Amyloid	6	2:4	18 ± 8	16 ± 7	7.5 ± 1.8	3/6	5/6	385 ± 144
Unclassifiable glomerular	3	1:2	140 ± 20	26 ± 15	4.7 ± 3.8	2/2	2/2	202 ± 142
Non-glomerular disease (36 cases)								
ATN	7	2:5	68 ± 25	5 ± 2	0.8 ± 0.3	4/6	0/5	537 ± 87
Vascular disease	2	1:1	108 ± 24	5 ± 2	0.9 ± 0.5	2/2	1/2	379 ± 295
Chronic pyelonephritis	11	7:4	136 ± 9	34 ± 18	2.2 ± 1.0	8/10	2/10	538 ± 131
Chronic tubulo-interstitial disease	8	6:2	112 ± 20	6 ± 1	1.5 ± 0.9	4/8	3/7	878 ± 192
Miscellaneous (non-glomerular)	8	4:4	94 ± 19	8 ± 3	1.8 ± 0.6	5/8	5/8	614 ± 221

[a] Owner's estimate of duration of clinical illness.
[b] Maximum urinary protein recorded during illness.
[c] Urinary FDP > 2 μg/mliter. Hematuria and FDP–number of positive out of total cases tested.
* No sample.

quently, 51 cases were examined for IgA, and IgM by indirect immunofluorescence or immunoperoxidase using antisera to canine immunoglobulin raised in sheep (IgM) or rabbits (IgA) (Steward, A. P., Macdougall, D. F., in preparation).

Electron microscopy

Electron microscopy was performed on 25 cases. Tissue stored in buffered formalin, or obtained from paraffin blocks and subsequently de-waxed and rehydrated, was post-fixed in 2% phosphate buffered osmium tetroxide for 30 min at room temperature, post-stained in 2% uranyl acetate for 30 min and dehydrated. Glomeruli were selected from 0.5 μ sections stained with Toluidine Blue. Ultrathin sections were examined on a Phillips E.M. 300 electron microscope.

Interpretation and classification of renal pathology

Kidneys were examined by light microscopy independently by two renal pathologists (Dr. Cattell and Dr. Cook) without prior knowledge of the clinical details of each case. Kidneys with primary glomerular pathology were classified according to the criteria in the W.H.O. collaborative study for the Histological Classification of Renal Diseases [19]. The material was initially classified on the basis of light microscopy and immunohistochemistry. Electron microscopy was performed on representative cases from each morphological type of gn, or on cases where light microscopy was not definitive for diagnosis. In particular all cases with capillary wall thickening by light microscopy were examined by electron microscopy.

Statistics

Statistical analysis of the clinical data were carried out by non-parametric methods using the Chi-squared test (age, sex), Mann–Whitney U test (proteinuria) or the Wolf–Wolfowitz runs test (age, serum creatinine) [20].

Results

In one year in the participating practices 10,700 dogs were presented for primary vaccination. Assuming a mean age of seven years, and a 30% vaccination rate in the overall dog population, the population represented by the survey was in the order of 230,000 dogs. In one year 444 suspected cases of CCRD were referred by the 24 veterinary practices. One hundred and eleven of these cases were considered to have renal dysfunction following investigations (see **Methods**). Renal histological material was obtained from 76 of these 111 cases: three by renal biopsy and 73 postmortem kidneys. Fifty–six dogs had complete postmortems and 17 had limited postmortems. Histological material was not obtained from 35 of the 111 cases. There was no 'investigator' bias in this sampling: in the great majority of these cases, the owner of the dog did not agree to postmortem examination.

Table 1 summarizes the main pathological and clinical findings in 76 dogs with renal disease studied morphologically. Forty (52%) had glomerular diseases and 36 (48%) non-glomerular diseases. More than 20 different breeds were represented.

Clinical findings

The level of proteinuria was significantly higher in the group with glomerular diseases than in that with non-glomerular disease ($P < 0.00006$ Mann–Whitney U test, $U = 261$). The age, sex, level of creatinine, or presence of hematuria did not differ significantly between the two groups.

Morphology

Glomerular diseases. Focal gn (FGN) was found in five cases. These cases were classified on the basis of focal and/or segmental glomerular lesions, together with unaffected glomeruli or segments of glomeruli. Three cases were focal mesangial proliferative gn; one of these was examined by

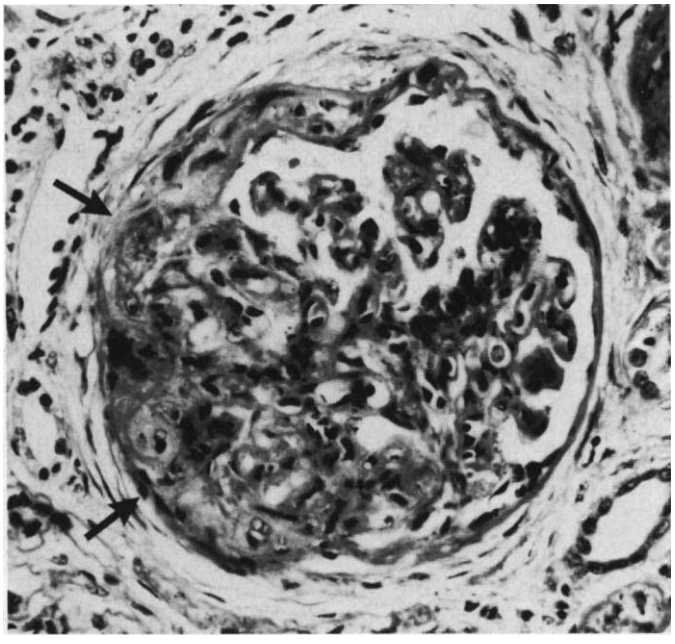

Fig. 1. *Glomerulus from a case of focal necrotizing gn, showing glomerular crescent (arrows).* MSB ×295.

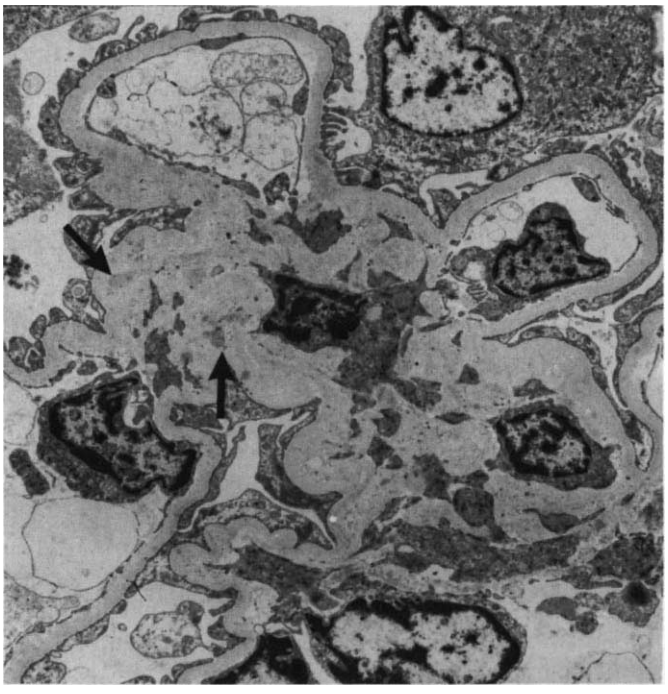

Fig. 2. *Electron micrograph of part of a glomerulus from a case of diffuse mesangial proliferative gn.* There is an increase in mesangial matrix and small mesangial deposits (arrows). ×4400.

electron microscopy and mesangial electron dense deposits were present. This case showed mesangial IgG and C3 in glomeruli on immunoperoxidase staining. The other two cases were focal necrotizing gn. Both were examined by electron microscopy. One showed fibrinoid necrosis of arterioles and arteries with multiple electron dense deposits on glomerular capillary walls, and the other had 48% crescents (Fig. 1) and rare small subepithelial and intramembranous electron dense deposits.

Diffuse mesangial proliferative gn (DMPGN) was found in eight cases. These cases showed diffuse and global mesangial hypercellularity. All eight were examined by electron microscopy. In all there was considerable diffuse increase in mesangial matrix with small numbers of electron dense deposits (Fig. 2) and in three cases, rare subendothelial and intramembranous deposits were also present. Seven cases were examined by immunoperoxidase staining. One had mesangial IgG deposits, one had capillary wall IgG, and two had capillary wall IgG, IgM and C3. No case had predominant IgA.

Diffuse endocapillary proliferative gn (DEPGN) was found in two cases. Glomeruli were enlarged and globally hypercellular with intraluminal cell increase (Fig. 3). One examined by electron microscopy showed large numbers of intraluminal monocytes and polymorphs. The electron dense deposits were mainly mesangial (Fig. 4), with rare isolated subepithelial electron dense deposits. The other case (not examined by electron microscopy) had multiple large recent renal infarcts in addition to gn; glomerular deposits of IgG, IgM and C3 were present on capillary walls by immunoperoxidase. At postmortem, a bacterial endocarditis and an acute osteomyelitis of the left turbinate bone were found.

Diffuse mesangiocapillary gn (membranoproliferative gn) (MCGN-Type I) was found in eight cases. Glomeruli were enlarged and lobulated, with a global increase in cellularity, and mesangial cell interposition (Fig. 5). Varying numbers were

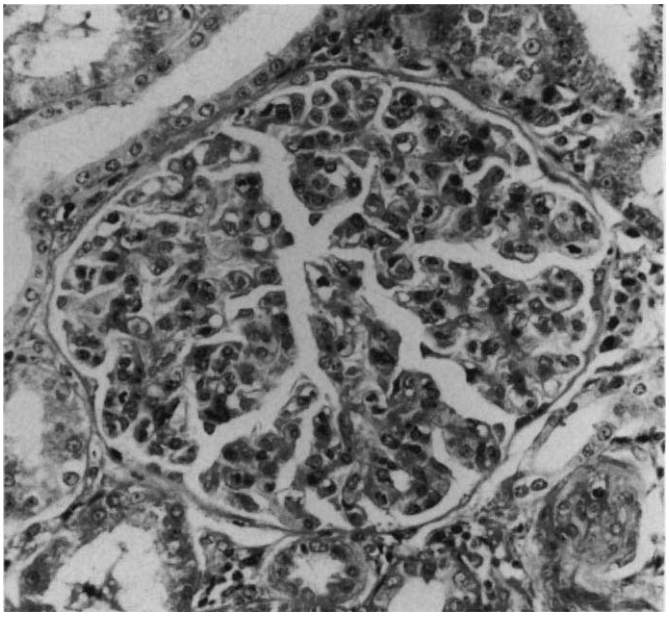

Fig. 3. *Glomerulus from a case of diffuse endocapillary proliferative gn, with global hypercellularity.* H & E ×295.

obsolete. In some there were small fibro-cellular crescents. Six cases were examined by electron microscopy. In these there was increased cellularity, capillary wall thickening due to mesangial cell interposition, and numerous subendothelial and mesangial electron dense deposits (Fig. 6). In three there were also subepithelial deposits (Fig. 7). In one case the deposits were predominantly intramembranous. In one, mononuclear-

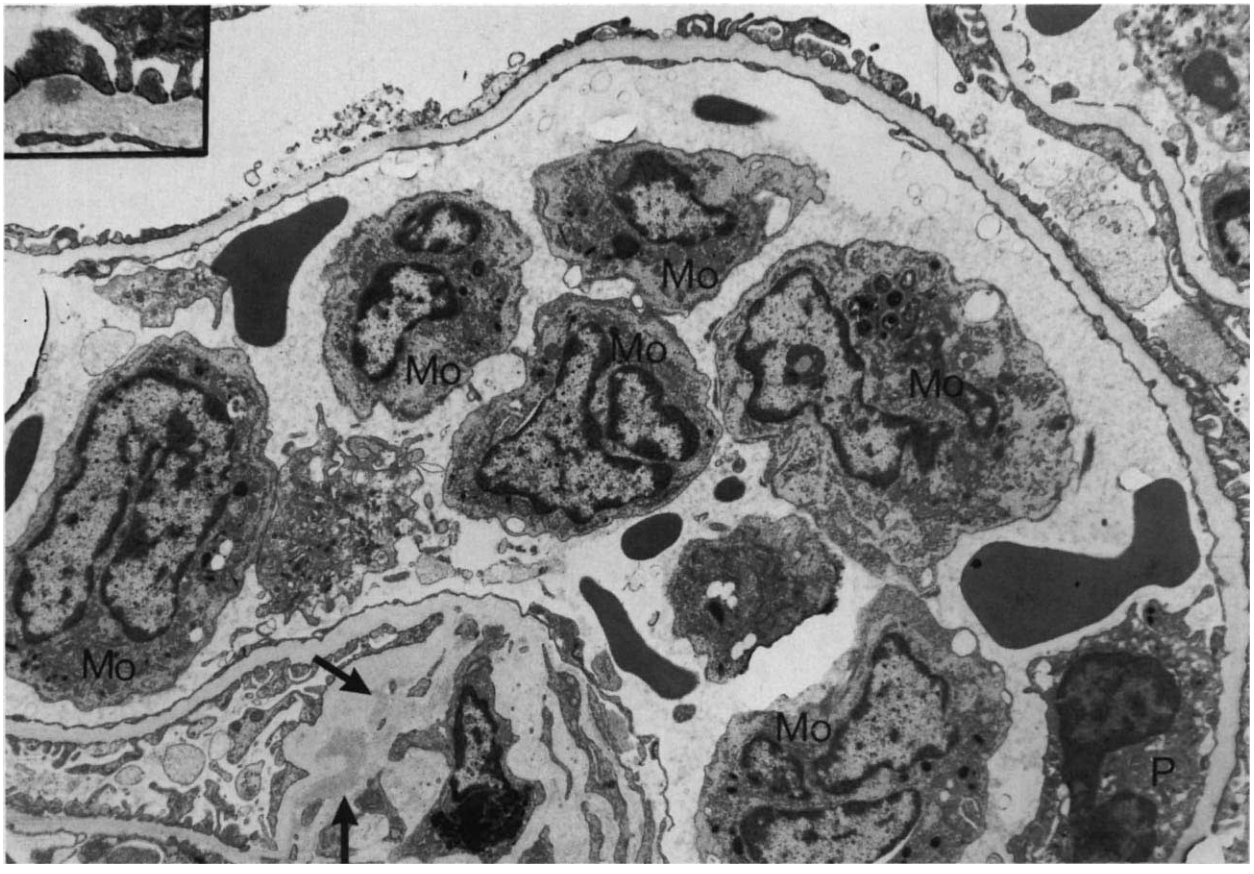

Fig. 4. *Electron micrograph of a glomerular capillary loop from the same case as Figure 3.* Monocytes (MO) and a polymorph (P) are present in the capillary lumen. There are small mesangial deposits (arrows). ×5200. Insert at top left shows small subepithelial deposit. ×12600.

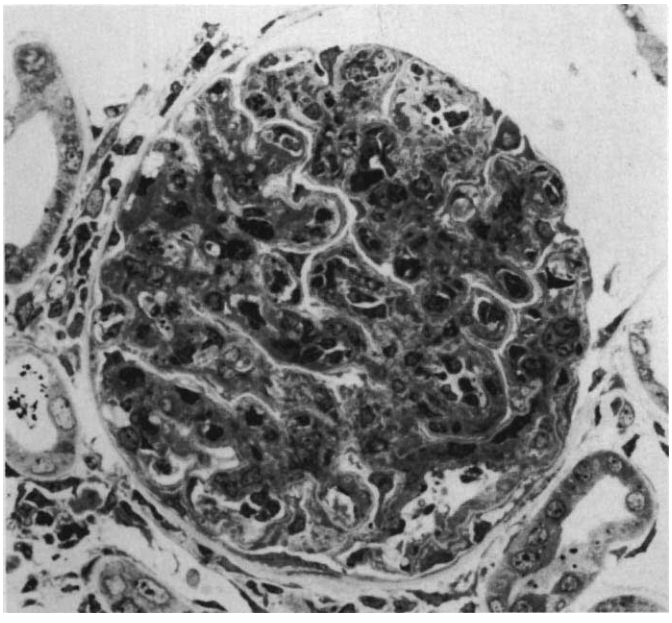

Fig. 5. *Glomerulus with global hypercellularity and capillary wall thickening from a case of mesangiocapillary gn.* 0.5 μ section. Azure II stain ×295.

cells and polymorphs were present in capillary lumens. Of the four cases with positive immunoperoxidase staining, two had capillary wall IgG, IgA and C3, one had capillary wall IgA, IgM and C3, and one had mesangial IgM alone.

Diffuse crescentic gn (DCGN) was found in one case. In this case the majority of glomeruli contained cellular crescents with fibrin in Bowman's space and collapse of underlying glomerular tufts. There was severe tubulo-interstitial scarring. Blood vessels were normal. Immunoperoxidase staining showed granular capillary wall IgA deposits.

Diffuse sclerosing gn (DSGN) was found in seven cases. In all these kidneys the majority of glomeruli were obsolete or showed progressive scarring with mesangial matrix increase, collapse of capillary walls, adhesions and some hyaline deposits. There was variable hypercellularity. In one case, there were vascular lesions resembling human benign hypertensive changes. Four cases were examined by electron microscopy. One showed non-specific capillary wall thickening; one showed mesangial electron dense deposits and two with a nodular appearance by light microscopy failed to show amyloid fibrils or light chain structures, and in one of these there were numerous subendothelial and mesangial deposits and segmental capillary wall IgM by immunoperoxidase staining.

Amyloid (AM) was found in six cases. Amyloid deposits positive with Congo Red were seen in glomeruli, vessels and interstitium.

Unclassifiable (UN) was found in three cases. In two cases of advanced chronic gn there was generalized capillary wall thick-

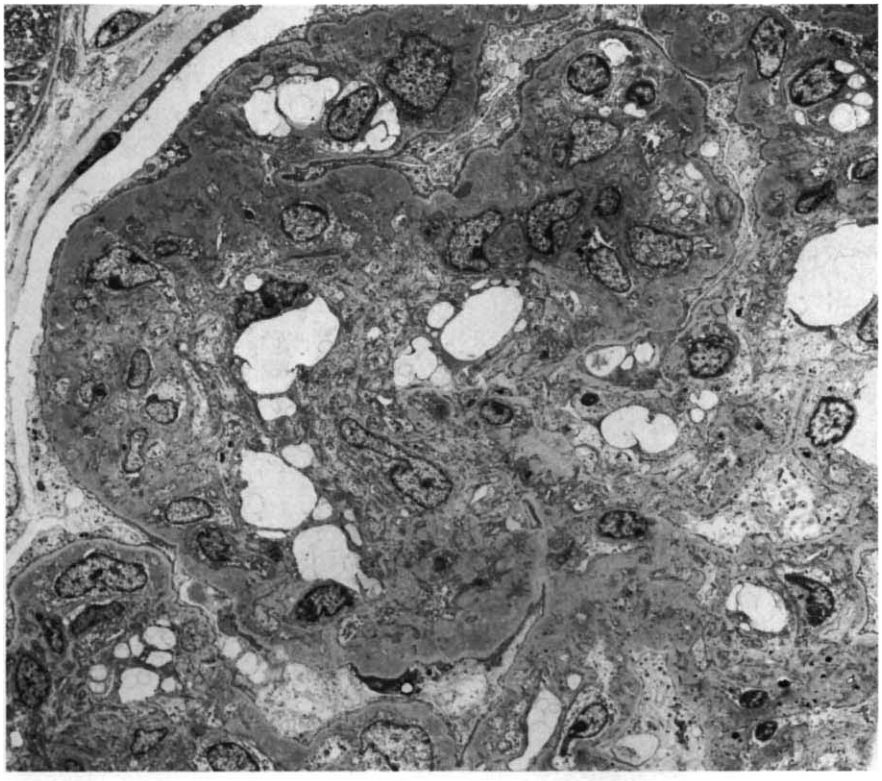

Fig. 6. *Low power electron micrograph of part of a glomerulus from a case of mesangiocapillary gn, showing increased mesangial cells and large subendothelial deposits.* ×1700.

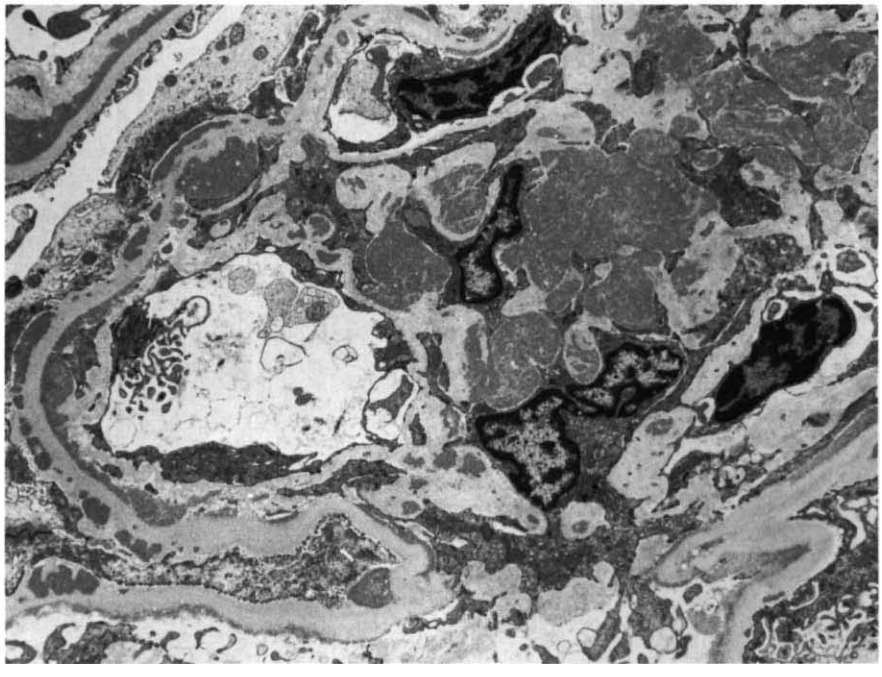

Fig. 7. *Electron micrograph of subepithelial, subendothelial and mesangial deposits in glomerulus from a case of mesangiocapillary gn.* ×5000.

ening with plexiform splitting of basement membranes (Fig. 8). There was little glomerular hypercellularity. In one of these there was also a subendothelial lucent zone and subendothelial electron dense deposits; capillary wall IgA was detected by immunoperoxidase. In the second there were rare mesangial deposits. (Lesser degrees of plexiform capillary wall thickening with lacunar spaces were seen in several other dogs with advanced gn). In the third case, the glomeruli showed a global increase in mesangial matrix with no increase in cellularity and no deposits by electron microscopy but capillary wall IgG and C3 were demonstrated by immunoperoxidase staining.

Nonglomerular diseases. Acute tubular necrosis was found in seven cases. In these cases acute tubular necrosis was the predominant or only pathology. One, however, showed glomer-

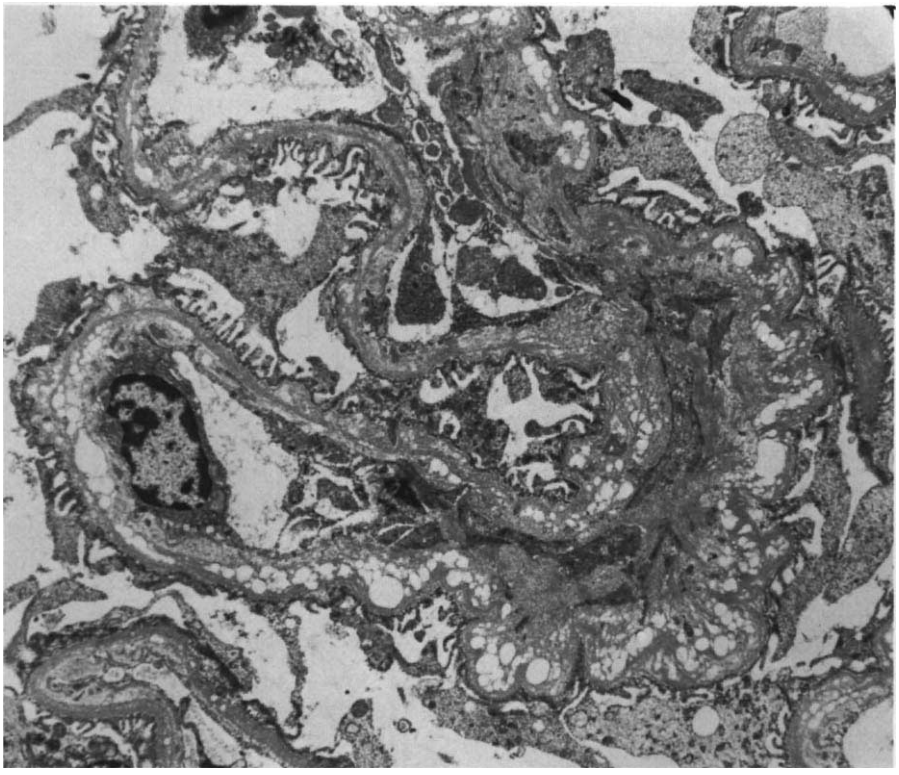

Fig. 8. *Electron micrograph of plexiform glomerular capillary wall thickening in a case of unclassifiable chronic gn.* ×6600.

ular capillary wall IgG deposition by immunoperoxidase. In many other cases, particularly in dogs in terminal renal failure, some degree of acute tubular necrosis was also present.

Vascular disease was found in two cases. One case had bilateral severe renal infarction, which was probably due to post-operative extra–renal causes. The other was an end–stage kidney with arteriolar and arterial intimal thickening, occasional areas of fibrinoid necrosis, and calcification in some large arteries. There was no evidence of arteritis, and this case was presumed hypertensive. Immunoperoxidase staining was negative.

Chronic pyelonephritis was found in 11 cases. In these there were interstitial and pelvic mononuclear cell infiltration and coarse cortical and medullary scarring. Immunoperoxidase staining was negative.

Chronic tubulo-interstitial disease was found in eight cases. This group had chronic tubular atrophy, interstitial fibrosis and mononuclear cell infiltrates without evidence of pelvic inflammation. There was focal glomerular obsolescence in scarred areas. Immunoperoxidase staining showed glomerular IgG in two cases. One case in addition showed papillary necrosis; this dog had a history of arthritis treated with intermittent analgesics. Immunoperoxidase was negative. Another case showed severe focal cortical scarring and extensive medullary fibrosis with areas of complete tubular loss. This was possibly a second case of papillary necrosis with scarring. Immunoperoxidase was negative.

There were eight miscellaneous types of non-glomerular disease. They were three cases of renal cell adenocarcinoma, one case with toxocaral larvae in the renal cortex, one case of unclassifiable focal cortical scarring, one kidney with leukemic infiltrates and two end–stage kidneys with diffuse cortical fibrosis but little evidence of inflammation. Immunoperoxidase staining was negative in this group apart from two of the carcinoma cases, one of which had glomerular IgG and one IgM.

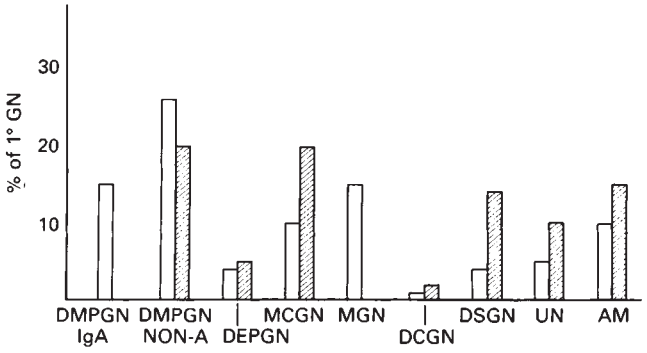

Fig. 9. *Relative incidence (as % of primary gn) of different morphological types of gn in dogs and humans.* Symbols are: □ humans; ▨ dogs. (Abbreviations in text).

Comparison with human gn

Figure 9 is a comparison between the types of gn in these dogs and the incidence of different types of gn in human renal biopsies. As no published data on humans were available for this purpose, the figures for human gn were taken from 259 consecutive renal biopsies examined by light and electron microscopy and diagnosed as primary gn at St. Mary's Hospital, London, W2 (1977–1983). Human cases of minor glomerular

abnormality, focal gn and membranous gn due to drug therapy were excluded (see **Discussion**) as were the five dogs with focal gn. There were no cases of mesangial IgA disease or membranous gn in the dogs. The incidence of diffuse mesangial proliferative gn (not IgA-associated), diffuse endocapillary gn, diffuse crescentic gn, and unclassifiable glomerular disease were comparable, while the incidences of mesangiocapillary gn, diffuse sclerosing gn, and amyloid were greater than in the human material.

Extra–renal lesions

Seven dogs with glomerular disease and 14 dogs with non-glomerular disease had extra–renal lesions other than those which could be attributed to uremia. In the glomerular group three had neoplasms, two had chronic liver disease, one had endocarditis, and one had a monoclonal gammopathy.

Serology

DNA binding and C3 were measured in the eight dogs with mesangiocapillary gn and none had a raised DNA binding or low C3. One dog in the unclassified glomerular disease group had titres of canine adenovirus antibody suggesting recent infection. One dog (miscellaneous—non-glomerular) had a raised leptospira titre suggesting recent contact with L. javanica (a serovar of leptospira not previously associated with clinical disease in the U.K.).

Discussion

Clinical findings

There was good evidence from the proportion of confirmed renal cases, 111 out of 444 suspected cases of CCRD, that participating practices had, as requested, sampled suspected cases and avoided bias towards particular clinical syndromes. These results suggest that the clinical criteria selected were sufficiently wide to result in the referral of the great majority of cases of clinical renal disease. With a high proportion of cases in advanced renal failure (Table 1) it was not possible to associate particular clinical findings with different categories of gn. Despite this, total proteinuria and urinary fibrin degradation products distinguished between glomerular and non-glomerular disease with the highest levels of proteinuria in the dogs with amyloid.

There was no clear evidence of any predisposition to renal disease related to sex or breed. The ages of the animals were not significantly different between glomerular and non-glomerular groups, but it was notable that 58% of dogs were 120 months or over, an age range where the proportion of dogs in the whole dog population is falling significantly. Any comparison with human data is complicated by the difference in life span between the species and the generally accepted variation in the longevity of different breeds of dog.

Renal pathology

The results showed that in dogs, as in humans, glomerular disease is a common cause of chronic renal disease accounting for 52% of cases. Forty–eight percent of cases were non-glomerular diseases. Interstitial nephritis, defined as chronic tubulo-interstitial disease without evidence of gn or pyelonephritis (pelvic inflammation) [21] was less common than in earlier reports [1, 2].

Morphological types of glomerular disease

Of the 40 cases of canine glomerular disease, 31 were classifiable as glomerulonephritis by currently accepted W.H.O. criteria used for human gn [19] and six were amyloid. A classification similar to that of the W.H.O. has recently been proposed for animals by Winter and Majid [22]. Examples of mesangial proliferative gn, focal gn, diffuse endocapillary gn, mesangiocapillary gn, crescentic gn and chronic sclerosing gn were identified. There were no cases of IgA-associated mesangial proliferative gn (Berger's disease), membranous nephropathy, minor glomerular abnormality or focal glomerulosclerosis. The rarity of hypertensive–type vascular lesions which are frequent in human chronic renal disease was notable. Mesangiocapillary gn has frequently been reported as a common type of canine gn [5, 7, 8, 10, 14]. The histology showed typical hypercellularity, and capillary wall thickening due to mesangial interposition, and electron microscopy showed large electron dense deposits. An unusual feature in some of the dogs was the large size of the mesangial deposits in comparison with human gn. There were two cases of diffuse endocapillary proliferative gn, which has not previously been separated from other types of 'proliferative' gn in the dog. Most striking was an absence of membranous gn, a morphological type which might have been expected in our series as it has been reported as relatively common in several series of canine gn [8–10, 23, 24]. In some of these previous series, electron microscopy was not performed so it is possible that membranous capillary wall changes have been overestimated. In our survey all cases with capillary wall thickening by light microscopy were additionally examined by electron microscopy, but no case with predominantly epimembranous deposits was found. However, two unclassifiable cases had basement membranes thickened and split with a vacuolated appearance similar to that described by Murray and Wright [8] in their cases of advanced membranous gn. No cases of Berger's IgA nephropathy were found. Possibly this type of gn, which is common in man, does not occur in dogs.

Comparison of morphological types of gn with human gn

It was of some interest to attempt a comparison between the incidence of different types of canine gn found in the survey with that found in humans. There are clearly a number of variables and biases in such a comparison, in particular the inevitable bias towards severe or end–stage renal diseases in the dogs. For this reason human figures for minor glomerular abnormalities were excluded as it was felt that the design of the dog survey would not detect most cases of this disease in the dog. In fact, no dog with significant proteinuria came into the category of minor glomerular abnormalities morphologically. Some types of gn (such as mesangial proliferative gn, diffuse endocapillary gn and diffuse crescentic gn) were apparently similar in incidence to humans, and the incidence of mesangiocapillary gn seemed greater. Three of the most important types of human gn, namely membranous gn, IgA nephropathy, and focal segmental glomerulosclerosis were not represented in the survey.

Etiological factors

In only one case, that of bacterial endocarditis, was a clear cause for the gn identified. Experimentally diffuse endocapillary proliferative gn has been induced in dogs in a model of staphylococcal endocarditis [25]. Serological tests did not identify SLE [26, 27] or hypocomplementemic-associated MCGN. One case of possible adenovirus infection [28] and one of leptospira infection were identified in the dogs with glomerular disease. None of the dogs with pyelonephritis or chronic tubulo-interstitial disease had titres suggesting current leptospira infection. Dirofilarial infection, a known cause of gn in dogs [29], has not been reported in the indigenous dog population of the United Kingdom. Murray and Wright [8] have previously reported an incidence of 70% extra-renal lesions associated with canine gn [8] of which 40% were malignant neoplasia. Extra-renal lesions were found only in seven of our 34 gn cases. The only lesions in these dogs which sometimes have an association with gn in humans were the cases of neoplasia (four cases) and cirrhosis (one case). We have not performed elution or antibody studies on these cases for possible pathogenic antigens. The cause of the cases of amyloid is not clear, although in one there was a neoplasm in the liver and spleen which was not examined histologically and in another, a renal adenocarcinoma. Immunohistological typing of the amyloid protein has not been carried out. Only AA type amyloid has been reported in the dog [30].

This prospective survey of cases of canine chronic renal disease from an outbred dog population in a defined geographical area clearly shows that glomerulonephritis is a common cause of chronic renal disease in the dog. It is the first series showing the relative incidence of gn compared with non-glomerular disease and the first series where the accepted W.H.O. criteria for the classification of morphological types of gn has been applied to animals.

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